Hydroborations: A New Convenient Route for the Preparation of 4-Alkyl- (or 4-Aryl)chroman-3-ones from 4-Alkyl- (or 4-Aryl)-2*H*-chromenes

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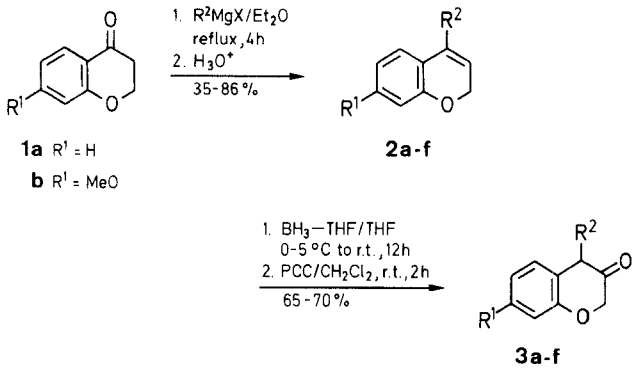
Hydroboration followed by pyridinium chlorochromate oxidation of 4-alkyl- and 4-aryl-2*H*-chromenes [4-alkyl- and 4-aryl-(2*H*)-1-benzopyrans] lead to the corresponding 4-substituted chroman-3-ones [4-substituted (2*H*)-1-benzopyran-3(4*H*)-ones] in good yields.

The chroman-3-ones are starting intermediates for the preparation of various biological and therapeutical agents. They are used for the synthesis of rotenones.[1-4] anti-juvenile hormone[5-7] and 3-aminochromans presenting potential antiestrogen,[8] dopaminergic,[9] serotoninergic,[10] myorelaxant[11] and antipsychotic properties.[12] As part of a research program is connection with the synthesis of potential biologically active compounds, we required large amounts of various substituted 4-alkyl- and 4-arylchroman-3-ones.



2, 3	R^1	R^2	2, 3	R^1	R^2
a	H	Me	**d**	H	4-$MeOC_6H_4$
b	H	Et	**e**	MeO	Ph
c	H	Ph	**f**	MeO	4-$MeOC_6H_4$

Scheme

An extensive survey of the literature[13] showed that a variety of routes had been developed for the preparation of these derivatives. However, they often involve multistep syntheses, lacking in generality and leading to mixtures or to low yields. The availability of a new general and convenient method for the preparation of substituted 4-alkyl- and 4-arylchroman-3-ones would thus be of interest. We therefore decided to convert the 4-alkyl or 4-aryl-2*H*-chromenes **2a–f** (Table 1), prepared via a Grignard reaction of the known chroman-4-ones **1a–b**, to the corresponding 4-substituted chroman-3-ones **3a–f** (Scheme), using the hydroboration–oxidation.[14,15] This reaction has previously been used for the preparation of aldehydes and ketones,[16,17] 1-substituted indan-2-ones,[18] 1-substituted 3,4-dihydronaphthalen-2(1*H*)-ones[19] and substituted derivatives of chroman-4-ones, isoflavanones and homoisoflavanones.[20-25]

Table 2 shows the yields and physicochemical data for derivatives **3a–f** (after purification by column chromatography) prepared by this method. Structures were established by IR and ^{1}H-NMR spectroscopy of the isolated products. Due to their relative instability,[26,33] all the compounds were converted to more stable 2,4-dinitrophenylhydrazone (DNPH) derivatives (correct microanalysis).

This study indicates that it is now possible to prepare conveniently 4-alkyl- or 4-arylchroman-3-ones with satisfactory yield, via hydroboration–pyridinium chlorochromate (PCC) oxidation of appropriately 4-substituted 2*H*-chromenes.

Melting points are uncorrected. Glassware was dried at 100 °C in an oven prior to use. BH_3-THF is commercially available (Aldrich). Column chromatography was performed on silica gel (Merck 60, 70–230 mesh). THF was distilled from benzophenone

Table 1. 4-Substituted 2*H*-Chromenes **2a–f** Prepared

Product	Yield (%)[a]	mp (°C)	Molecular Formula[b] or Lit. bp (°C)/mbar	IR ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
2a	59	oil	102/8[26,27]	2850, 1630[c]	2.1 (s, 3H, CH_3), 4.8 (d, 2H, J = 4, H-2), 5.6 (t, 1H, J = 4, H-3), 6.7–7.4 (m, 4H_{arom})
2b	35	oil	125/10[28]	2830, 1620[c]	1.2 (t, 3H, J = 8, CH_3CH_2), 2.5 (q, 2H, J = 8, CH_2CH_3), 4.85 (d, 2H, J = 4, H-2), 5.65 (t, J = 4, H-3), 6.8–7.3 (m, 4H_{arom})
2c	81	oil	137/0.6[28]	3060, 2860, 1600[c]	4.75 (d, 2H, J = 4, H-2), 5.7 (t, 1H, J = 4, H-3), 6.6–7.5 (m, 9H_{arom})
2d	86	92	$C_{16}H_{14}O_2$ (238.3)	3060, 2820, 1620[d]	3.8 (s, 3H, OCH_3), 4.8 (d, 2H, J = 4, H-2), 5.8 (t, 1H, J = 4, H-3), 6.6–7.4 (m, 8H_{arom})
2e	79	oil	115–118/1[29]	3060, 2960, 1620[c]	3.7 (s, 3H, OCH_3), 4.7 (d, 2H, J = 4, H-2), 5.55 (t, 1H, J = 4, H-3), 6.2–7.4 (m, 8H_{arom})
2f	79	105	$C_{17}H_{16}O_3$ (268.3)	3060, 2850, 1630[d]	3.8 (2s, 6H, OCH_3), 4.8 (d, 2H, J = 4, H-2), 5.7 (t, 1H, J = 4, H-3), 6.5–7.7 (m, 7H_{arom})

[a] Yield of isolated product.
[b] Satisfactory microanalysis obtained: C ±0.29, H ±0.28.
[c] NaCl cell.
[d] KBr plate.

Table 2. 4-Substituted Chroman-3-ones **3a–f** Prepared

Product	Yield (%)[a]	mp of DNPH (EtOH) (°C)	Mol. Formula (DNPH)[b] or Lit. mp (DNPH) (°C) or bp (°C)	IR (NaCl) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	68	167	102–103/0.2[30]	3400, 1620	1.2 (d, 3H, J = 5, CH_3), 2.7 (q, 1H, J = 5, H-4), 4.2 (s, 2H, H-2), 6.7–7.4 (m, 4H_{arom})
3b	66	162	$C_{17}H_{16}N_4O_5$ (357.1)	3360, 2970, 1560	1.05 (t, 3H, J = 4, CH_3CH_2), 1.65 (m, 2H, CH_2CH_3), 2.65 (m, 1H, H-4), 4.1 (s, 2H, H-2), 6.7–7.2 (m, 4H_{arom})
3c	65	170	170[26,31,32]	3400, 2930, 1580	3.9–4.3 (m, 3H, H-2, H-4), 6.8–7.4 (m, 9H_{arom})
3d	70	173	$C_{22}H_{18}N_4O_6$ (434.4)	3380, 1600	3.6 (s, 1H, H-4), 3.8 (s, 3H, OCH_3), 4.2 (s, 2H, H-2), 6.6–7.8 (m, 8H_{arom})
3e	62	201	$C_{22}H_{18}N_4O_6$ (434.4)	3400, 2940, 1620	3.8 (s, 3H, OCH_3), 3.9–4.2 (m, 3H, H-2, H-4), 6.5–7.4 (m, 8H_{arom})
3f	65	154	$C_{23}H_{20}N_4O_7$ (464.4)	3400, 1620	3.6 (s, 1H, H-4), 3.8 (2s, 6H, OCH_3), 4.2 (s, 2H, H-2), 6.5–7.4 (m, 7H_{arom})

[a] Yield of isolated product.
[b] Satisfactory microanalysis obtained: C ±0.26, H ±0.31, N ±0.23.

ketyl prior to use. IR spectra were recorded on a Perkin Elmer 177 spectrophotometer and ^{1}H-NMR spectra on a Varian T 60 spectrometer.

7-Methoxy-4-(4-methoxyphenyl)-2*H*-chromene [7-Methoxy-4-(4-methoxyphenyl)-(2*H*)-1-benzopyran, 2f]; Typical Procedure A:
To a dry N_2 flushed 250 mL round bottom flask fitted with a magnetic stirring bar and a reflux condenser protected with a $CaCl_2$ drying tube, are introduced dry Mg turnings (1.0 g, 40 mmol) and a crystal of I_2. A solution of 4-bromoanisole (1.12 g, 6 mmol) in dry Et_2O (50 mL) is added dropwise. The mixture is refluxed (4 h) and allowed to cool to r.t. The 7-methoxychroman-4-one (**1b**; 0.712 g, 4 mmol) dissolved in dry Et_2O (50 mL) is then added slowly and the mixture refluxed for 4 h. The reaction is allowed to cool to r.t. and sat. aq NH_4Cl (100 mL) is added to the stirred ethereal solution over a period of 15 min. The Et_2O layer is separated and the aqueous layer is extracted with Et_2O (3 × 50 mL). The combined organic solutions are then washed with brine to neutrality and dried (Na_2SO_4). The solvent is evaporated under reduced pressure and 20% (v/v) aq H_2SO_4 (50 mL) is added to the residue. After refluxing for 2 h, the Et_2O layer is separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic solutions are then washed with brine to neutrality and dried (Na_2SO_4). The solvent is evaporated and the crude product is purified by column chromatography (eluent CH_2Cl_2) to give **2f**; yield: 0.85 (79%).

The other 4-aryl-2*H*-chromenes **2c–e** are prepared by the same technique. For the preparation of the 4-alkyl-2*H*-chromenes **2a–b**, the reaction of the alkylmagnesium halides is performed with a reflux time of 2 h. Yields and physicochemical data are given in Table 1.

7-Methoxy-4-(4-methoxyphenyl)chroman-3-one [7-Methoxy-4-(4-methoxyphenyl)-(2*H*)-1-benzopyran-3(4*H*)-one, 3f]; Typical Procedure B:
To a dry N_2 flushed 100 mL round bottom flask, fitted with a magnetic stirring bar and a reflux condenser equipped with a connecting tube leading to a mercury bubbler, a 1 M solution of BH_3-THF (4.0 mL, 4.0 mmol) is added dropwise with a syringe via a septum inlet to a cooled solution (0–5 °C) of **2f** (0.8 g, 3.0 mmol) dissolved in dry THF (50 mL). The reaction is allowed to warm up to r.t and stirring is continued overnight (12 h). The THF is evaporated and CH_2Cl_2 (20 mL) is added. The oxidation is carried out by dropwise addition of a suspension of pyridinium chlorochromate (PCC) (2.6 g, 12 mmol) in CH_2Cl_2 (20 mL) stirring continued (2 h) at r.t. The mixture is diluted with Et_2O (200 mL) and filtered over anhydr. Na_2SO_4 (10 g). The Na_2SO_4 pad is then washed with Et_2O (3 × 50 mL). The combined organic solutions are evaporated and the product is separated by column chromatography (eluent CH_2Cl_2/EtOH, 95:5) to give of **3f**. Yield: 0.55 g (65%).

Preparation and isolation of the other chroman-3-ones **3a–e** is performed as described in the Typical Procedure B, from the corresponding 2*H*-chromenes **2a–e**. Yields and physico-chemical data are given in Table 2.

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